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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
OLSON, ERIC	
ART UNIT	PAPER NUMBER
1623	
MAIL DATE	DELIVERY MODE
06/09/2010	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/627,358	MIGALY, PETER	
	Examiner	Art Unit	
	ERIC S. OLSON	1623	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 March 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-8,10-38,41-43,48-64 and 66-147* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-8,10-38,41-43,48-64 and 66-147* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on March 15, 2010 has been entered.

Detailed Action

This office action is a response to applicant's communication submitted March 15, 2010 wherein claims 1, 2, 42, 48, 53, 54, 59, 100, 122, 123, 130, 134-140, 142, and 144 are amended and claim 9 and 65 are cancelled. This application claims benefit of provisional application 60/319436, filed July 30, 2002.

Claims 1-8, 10-38, 41-43, 48-64, and 66-147 are pending in this application.

Claims 1-8, 10-38, 41-43, 48-64, and 66-147 as amended are examined on the merits herein.

Applicant's amendment, submitted March 15, 2010, with respect to the rejection of instant claim 65 under 35 USC 112, first paragraph, for introducing new matter into the disclosure, has been fully considered and found to be persuasive to remove the rejection as claim 65 has been cancelled. Therefore the rejection is withdrawn.

Applicant's arguments, submitted March 15, 2010, with respect to the rejection of instant claims 1-9, 11-12, 37, 38, 41-43, 48-50, 53-71, 96-103, 126, 131-145, and 147 under 35 USC 112, first paragraph, for lacking enablement for all of the claimed classes of compounds, have been fully considered and found to be persuasive to remove the rejection as all of the claimed classes of compounds are known in the art to be useful for treating patients suffering from depression and would have been available to one skilled in the art. Therefore the rejection is withdrawn.

Applicant's arguments, submitted March 15, 2010, with respect to the rejection of instant claims 1, 2, 4, 6, 10-15, 18, 22, 26, 30, 36-38, 41, 42, 48, 51-53, 56, 58-60, 109-118, 124, 125, and 140-143 under 35 USC 103(a) for being obvious over Tollefson et al. '921, has been fully considered and found to be persuasive to remove the rejection as a review of the prior art indicates that the clinical trial described by Tollefson et al. involved schizophrenic patients. Specifically, the non-patent reference Tollefson et al. (Reference included with PTO-892) discloses further information concerning the same clinical trial and indicates that he subjects were schizophrenic. Therefore the rejection is withdrawn.

Applicant's amendment, submitted March 15, 2010, with respect to the rejection of instant claims 1-3, 9, 11-15, 37, 38, 41-43, 48, 49, 53-62, 69-74, 96-105, 129, 142, and 145 under 35 USC 103(a) as being obvious over Robertson et al. in view of Merck, has been fully considered and found to be persuasive to remove the rejection as the

claims have been amended to exclude methods using typical antipsychotics. Therefore the rejection is withdrawn.

Applicant's amendment, submitted March 15, 2010, with respect to the rejection of instant claims 106-107 under 35 USC 103(a) as being obvious over Robertson et al. in view of Berman, has been fully considered and found to be persuasive to remove the rejection as the claims have been amended to exclude methods using typical antipsychotics. Therefore the rejection is withdrawn.

Applicant's amendment necessitates the following new grounds of rejection:

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 69 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. This claim specifies that the antipsychotic drug is selected from the group consisting of perphenazine, trifluoroperazine, zotepine, fluphenthixol, amisulpride, and sulpride. These are typical antipsychotic drugs. However, this claim depends from claims 55 and 57, which depend from claims 1 and 2, which require that the antipsychotic be an atypical antipsychotic or dopamine system stabilizer. Therefore claim 69 contradicts the limitations of its parent claims, creating confusion as to what its true scope is and rendering the limitations of this claim indefinite.

The following rejections of record in the previous office action are maintained:

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 140, 141, 143, and 144 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicant's amendment submitted March 13, 2009 with respect to the aforementioned claims has been fully considered and but is deemed to insert **new matter** into the claims since the specification as originally filed does not provide support for a method comprising discussing all of the specific considerations recited in the claims with a patient. Although the specification and the priority document 60/319436 do disclose these factors as considerations for physicians to take into account in the treatment of depression, they do not teach or disclose discussing them with a patient. As the instant specification as filed contains no description of this method the specification as originally filed does not provide support for the subject matter of instant claims 140, 141, and 143. See *in re Smith*, 458 F.2d 1389, 1395, 173 USPQ 679, 683 (CCPA 1972).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-6, 11, 13, 37, 38, 41-43, 48, 49, 53, 54, 56, 58, 59, 119-121, 123, 126-129, 142, 145, and 146 are rejected under 35 U.S.C. 103(a) as being unpatentable over Howard. (US patent publication 2002/0123490, of record in previous action)

Howard discloses a combination of a serotonin reuptake inhibitor and an atypical antipsychotic, as well as a method for using this combination to treat obsessive compulsive disorder, psychosis, and depression. (p. 1, paragraph 0004) Depressive disorders treated include major depressive disorder, as well as atypical depression including anxiety. (p. 1, paragraph 0008) Anxiety is reasonably considered to be as cognitive distortion as it involves disordered cognitions such as overestimation of risk. Although treatment of refractory depression is a preferred embodiment, all depression including depression not found to be refractory, is included within the range of disorders to be treated. The amounts of each agent used are such that the combined effect has improved efficacy compared to either component individually. (p. 1 paragraph 0005) Atypical antipsychotics used in the invention include abaperidone, belaperidone, clozapine, iloperidone, olanzapine, perospirone, risperidone, sertindole, tiospirone, ziprasidone, zotepine, quetiapine, and blonanserin. (p. 7 paragraphs 0172-0198) The

two agents are to be administered in dosages of about 5-200 mg/day of the antipsychotic agent and about 2.5-500 mg/day of the serotonin reuptake inhibitor. (p. 8 paragraph 0233) The compounds can be administered by various dosage forms including oral administration. (p. 9 paragraphs 0235-0236) Howard does not specifically disclose a method wherein the therapeutic agents are administered as soon as possible.

It would have been obvious to one of ordinary skill in the art at the time of the invention to administer the therapy disclosed by Howard as an initial therapy and/or to administer it as soon as possible. One of ordinary skill in the art would have been motivated to practice the invention in this manner because Howard already discloses the treatment to be useful as a treatment for depression generally, and because it is standard practice in the art to administer a therapy promptly once it is indicated. One of ordinary skill in the art would reasonably have expected success because choosing a particular therapeutic regimen from among the various options available in the prior art is within the routine and ordinary level of skill in the art. Note that "as soon as possible" is an extremely broad limitation that would include practically any method wherein treatment was not deliberately delayed. Similarly, discussing the risks and benefits of a therapeutic method with a patient are part of the ordinary responsibility of a health care provider and are ordinary and routine in the art.

Thus the invention taken as a whole is *prima facie* obvious.

Claims 1-4, 6, 10-15, 18, 22, 26, 30, 36-38, 41-43, 48, 49, 51-63, 66, 70-74, 77, 81, 85, 89, 95-105, 109-122, 124, 126-130, and 142 are rejected under 35 U.S.C. 103(a) as being obvious over Chappell et al. (US patent application 10/001827, Pub. Number 2002/0094986 A1, of record in previous office action)

Chappell et al. discloses a method of treating depression, anxiety, or psychosis in a mammal by administering a combination of an antidepressant, a D4 receptor antagonist, (an antipsychotic) and a pharmaceutically acceptable carrier. (p. 1, left column, paragraph 0002) Note that anxiety is reasonably considered to be a cognitive distortion as it involves unreasonable patterns of thought, namely excessive or irrational worry and exaggeration of problems or threats. Phobias and panic disorders are also considered to be cognitive distortions. General types of antidepressants which can be used are listed in paragraph 0021 and include norepinephrine reuptake inhibitors, serotonin reuptake inhibitors, and monoamine oxidase inhibitors, among others, as described in instant claims 11-13. Selective serotonin reuptake inhibitors include fluoxetine, fluvoxamine, paroxetine, and sertaline. (p. 3, paragraph 0025) Norepinephrine reuptake inhibitors which may be used are listed in paragraph 0023 and include clomipramine among others, as in instant claims 14 and 15. Other useful antidepressants are listed in paragraph 0181 on p. 8. The compounds used in this invention may all be administered orally, as described by instant claim 38. (p. 22, paragraphs 0460-0462) Various dopamine D4 receptor antagonists can be used, as listed on pp. 15-21. In particular, p. 20, paragraph 0446 lists olanzapine as a useful D4 receptor antagonist. D4 receptor antagonists can be administered in a preferred dose

of about 5 to about 500 mg per day. (p. 22, paragraph 0459) Chappell et al. does not explicitly disclose a method of administering the claimed treatments as an initial treatment, as soon as possible, or upon presentation to a physician or other health care provider. Chappell et al. does not disclose a method where in the antipsychotic is administered in a dose of 2.5-10 mg olanzapine.

It would have been obvious to one of ordinary skill in the art at the time of the invention to administer the therapy disclosed by Chappell et al. as an initial therapy and/or to administer it as soon as possible. One of ordinary skill in the art would have been motivated to practice the invention in this manner because Chappell et al. already discloses the treatment to be useful as a treatment for depression generally, and because it is standard practice in the art to administer a therapy promptly once it is indicated. One of ordinary skill in the art would reasonably have expected success because choosing a particular therapeutic regimen from among the various options available in the prior art is within the routine and ordinary level of skill in the art.
It would also have been obvious to one of ordinary skill in the art at the time of the invention to practice the method of Chappell et al. using a dose of 5-10 mg of olanzapine per day. One of ordinary skill in the art would have been motivated to use this range, and would have reasonably expected success in doing so, because the range disclosed by Chappell et al. significantly overlaps with the range of the claimed invention, which is considered to represent Applicant's low dose regimen. When the claimed ranges "overlap or lie inside ranges disclosed by the prior art" a prima facie case of obviousness exists. See *In re Wertheim*, 541 F.2d 257, 191 USPQ 90 (CCPA

1976); *In re Woodruff*, 919 F.2d 1575, 16 USPQ2d 1934 (Fed. Cir. 1990). See MPEP § 2144.05 [R-1].

Further, discussing the risks and benefits of a therapeutic method with a patient are part of the ordinary responsibility of a health care provider and are ordinary and routine in the art.

Thus the invention taken as a whole is *prima facie* obvious.

Claims 106-108, 131-134, and 136-139 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chappell et al. (US patent application 10/001827, Pub. Number 2002/0094986 A1, of record in previous office action) in view of Berman et al. (Reference of record in previous action)

The disclosure of Chappell et al. is discussed above. Chappell et al. does not disclose a method in which the antidepressant is ketamine.

Berman et al. discloses that ketamine, which acts on the NMDA receptor, exerts antidepressant effects in human patients. (p. 351, second paragraph, right column, p. 352, left column, last paragraph, p. 353, right column, first paragraph)

It would have been obvious to one of ordinary skill in the art at the time of the invention to use ketamine as the antidepressant in the method of Chappell et al. One of ordinary skill in the art would have been motivated to practice the invention in this manner because Berman et al. reveals that ketamine is useful for the same purposes as the antidepressants recited by Chappell et al. One of ordinary skill in the art would

reasonably have expected success because Ketamine is already known to be useful as an antidepressant.

Thus the invention taken as a whole is *prima facie* obvious.

Claims 5, 16, 17, 20, 21, 24, 25, 28, 29, 32-35, 64, 75, 76, 79, 80, 83, 84, 87, 88, 91-94, 123, and 125 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chappell et al. (US patent application 10/001827, Pub. Number 2002/0094986 A1, of record in previous office action) as applied to claims 1-4, 6, 10-15, 18, 22, 26, 30, 36-38, 41-43, 48, 49, 51-63, 66, 70-74, 77, 81, 85, 89, 95-105, and 109-122, 124, and 126-30 above, and further in view of Schmidt et al. (Reference of record in previous action)

The disclosure of Chappell et al. is discussed above. Chappell et al. does not disclose a method using ziprasidone, risperidone, or quetiapine as the antipsychotic agent.

Schmidt et al. discloses the affinities of a number of antipsychotic drugs for the D4 receptor. (p. 198, table 1) In particular, ziprasidone, risperidone, olanzapine, and quetiapine are all shown to have affinity for the D4 receptor.

It would have been obvious to one of ordinary skill in the art at the time of the invention to use ziprasidone, risperidone, or quetiapine as the dopamine D4 antagonist in the invention of Chappell et al. One of ordinary skill in the art would have recognized that these compounds possess the same biological activity, namely D4 antagonism, required by the invention of Chappell et al., and can thus be used as therapeutic agents

in this invention. Applying a known therapeutic agent in this way to a known therapeutic method, is part or the ordinary and routine level of skill in the art.

Thus the invention taken as a whole is *prima facie* obvious.

Claims 5, 16, 20, 24, 28, 64, 75, 79, 83, 87, and 125 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chappell et al. (US patent application 10/001827, Pub. Number 2002/0094986 A1, of record in previous office action) as applied to claims 1-4, 6, 10-15, 18, 22, 26, 30, 36-38, 41-43, 48, 49, 51-63, 66, 70-74, 77, 81, 85, 89, 95-105, and 109-122, 124, and 126-30 above, and further in view of Roth et al. (Reference of record in previous action)

The disclosure of Chappell et al. is discussed above. Chappell et al. does not disclose a method using risperidone, trifluoroperazine, or zotepine as the antipsychotic agent.

Roth et al. discloses the affinities of a number of antipsychotic drugs for the D4 receptor. (p. 366, table 1) In particular, risperidone, olanzapine, trifluoroperazine and zotepine are all shown to have affinity for the D4 receptor.

It would have been obvious to one of ordinary skill in the art at the time of the invention to use risperidone, trifluoroperazine, or zotepine as the dopamine D4 antagonist in the invention of Chappell et al. One of ordinary skill in the art would have recognized that these compounds possess the same biological activity, namely D4 antagonism, required by the invention of Chappell et al., and can thus be used as

therapeutic agents in this invention. Applying a known therapeutic agent in this way to a known therapeutic method, is part or the ordinary and routine level of skill in the art.

Thus the invention taken as a whole is *prima facie* obvious.

Claims 1, 2, 4, 5, 6, 10-14, 16-18, 20-22, 24-26, 28-30, 32-38, 41-43, 48, 49, 51-64, 66, 70-77, 79-81, 83-85, 87-89, 91-105, 109-122, 124-129, and 145-147 are rejected under 35 U.S.C. 103(a) as being unpatentable over Pivac et al. (Reference included with previous action) in view of Merck (Reference of record in previous action)

Pivac et al. discloses that atypical antipsychotics such as risperidone or olanzapine, should be coadministered with selective serotonin reuptake inhibitors, because they produce a synergistic effect. (p. 236, left column, last paragraph, right column first paragraph) Pivac et al. does not disclose a therapeutic method using the specific SSRIs fluoxetine, paroxetine, sertaline, or fluvoxamine, or the atypical antipsychotics ziprasidone or quetiapine. Pivac et al. does not explicitly disclose a method of administering the claimed treatments as an initial treatment, as soon as possible, or upon presentation to a physician or other health care provider, or a method comprising administering a low dose of the antipsychotic.

Merck discloses a list of antidepressants useful for treating major depressive disorder. (p. 1534, table 189-6) These antidepressants include various antidepressants recited in the instant claims such as Clomipramine, fluoxetine, sertaline, paroxetine, and fluvoxamine. Merck et al. also discloses a listing of atypical antipsychotics, including

clozapine, risperidone, olanzapine, quetiapine, sertindole, and ziprasidone. (p. 1570, table 193-4)

It would have been obvious to one of ordinary skill in the art at the time of the invention to use the various SSRIs and atypical antipsychotics disclosed by Merck in the method of Pivac et al. One of ordinary skill in the art would have recognized that the specific compounds disclosed by Merck fall within the broad classes described by Pivac et al., and can thus be used in the disclosed method. Substituting these known prior art compounds in a known prior art method is well within the ordinary and routine level of skill in the art.

It would have been obvious to one of ordinary skill in the art at the time of the invention to administer the therapy disclosed by Pivac et al. as an initial therapy and/or to administer it as soon as possible. One of ordinary skill in the art would have been motivated to practice the invention in this manner because Pivac et al. and Merck already disclose the treatment to be useful as a treatment for depression generally, and because it is standard practice in the art to administer a therapy promptly once it is indicated. One of ordinary skill in the art would reasonably have expected success because choosing a particular therapeutic regimen from among the various options available in the prior art is within the routine and ordinary level of skill in the art.

Finally, it would have been obvious to one of ordinary skill in the art to administer the antipsychotic in a low dose. One of ordinary skill in the art would have been motivated to administer the lowest effective dose of the drug because of the well known side effects of typical antipsychotic drugs. One of ordinary skill in the art would have

reasonably been able to adjust the dosage of the compounds administered to achieve the optimal result while minimizing toxicity from the drugs themselves.

Similarly, discussing the risks and benefits of a therapeutic method with a patient are part of the ordinary responsibility of a health care provider and are ordinary and routine in the art.

Thus the invention taken as a whole is *prima facie* obvious.

Claims 1-4, 7, 8, 10-15, 19, 23, 27, 31, 36-38, 41-43, 48, 49, 51-63, 67, 68, 70-74, 78, 82, 86, 90, 95-105, 109-122, 124-130, and 145-147 are rejected under 35 U.S.C. 103(a) as being unpatentable over Jordan et al. (PCT international publication WO02/060423, reference of record in previous action) in view of Merck. (Reference of record in previous action) Jordan et al. discloses a method of treating a patient suffering from a disorder of the central nervous system associated with the 5-HT_{1A} receptor, comprising administering a compound having a given structure. (p. 15, lines 5-18) According to the Chemical Abstracts Registry entry 129722-12-9, (reference of record in previous action) this structure is aripiprazole. This compound is useful for treating various disorders of the central nervous system, for example major depression and melancholia, as well as various cognitive distortions including obsessive compulsive disorder, alcohol and drug addiction, and cognitive impairment. (p. 16, line 23 – p. 17, line 10) The preferred unit dosage form is 1-20 mg of active agent. (p. 18, lines 5-10) Jordan et al. does not disclose a method comprising administering aripiprazole in

combination with an antidepressant. Jordan et al. does not explicitly disclose a method of administering the claimed treatments as an initial treatment, as soon as possible, or upon presentation to a physician or other health care provider, or a method comprising administering 2.5-15 mg of aripiprazole.

Merck discloses a list of antidepressants useful for treating major depressive disorder. (p. 1534, table 189-6) These antidepressants include various antidepressants recited in the instant claims such as Clomipramine, fluoxetine, sertaline, paroxetine, and fluvoxamine.

It would have been obvious to one of ordinary skill in the art at the time of the invention to co-administer the antidepressants of Merck with the typical antipsychotics of Jordan et al. to a patient suffering from major depression either alone or complicated by any of the various cognitive distortions recited by Jordan et al. One of ordinary skill in the art would have recognized that these two therapies can be combined because they are both directed toward treating the same condition, namely major depressive disorder. Combining two known prior art therapies is well within the ordinary and routine level of skill in the art.

It would have been obvious to one of ordinary skill in the art at the time of the invention to administer the therapy disclosed by Jordan et al. as an initial therapy and/or to administer it as soon as possible. One of ordinary skill in the art would have been motivated to practice the invention in this manner because Jordan et al. and Merck already disclose the treatment to be useful as a treatment for depression generally, and because it is standard practice in the art to administer a therapy promptly once it is

indicated. One of ordinary skill in the art would reasonably have expected success because choosing a particular therapeutic regimen from among the various options available in the prior art is within the routine and ordinary level of skill in the art.

It would also have been obvious to one of ordinary skill in the art at the time of the invention to practice the method of Jordan et al. using a dose of 2.5-15 mg of aripiprazole per day. One of ordinary skill in the art would have been motivated to use this rang, and would have reasonably expected success in doing so, because the range disclosed by Jordan et al. significantly overlaps with the range of the claimed invention, which is considered to represent Applicant's low dose regimen. When the claimed ranges "overlap or lie inside ranges disclosed by the prior art" a prima facie case of obviousness exists. See *In re Wertheim*, 541 F.2d 257, 191 USPQ 90 (CCPA 1976); *In re Woodruff*, 919 F.2d 1575, 16 USPQ2d 1934 (Fed. Cir. 1990). See MPEP § 2144.05 [R-1].

Similarly, discussing the risks and benefits of a therapeutic method with a patient are part of the ordinary responsibility of a health care provider and are ordinary and routine in the art.

Thus the invention taken as a whole is *prima facie* obvious.

Claims 106-108, 131-133, and 135-139 are rejected under 35 U.S.C. 103(a) as being unpatentable over Jordan et al. (Reference of record in previous action) in view of Berman et al. (Reference of record in previous action) The disclosure of Jordan et al. is

discussed above. Jordan et al. does not disclose a method in which the antidepressant is ketamine.

Berman et al. discloses that ketamine exerts antidepressant effects in human patients. (p. 351, second paragraph, right column, p. 352, left column, last paragraph, p. 353, right column, first paragraph)

It would have been obvious to one of ordinary skill in the art at the time of the invention to use ketamine as an antidepressant in combination with a typical antipsychotic recited in the method of Jordan et al. One of ordinary skill in the art would have been motivated to practice the invention in this manner because Berman et al. reveals that ketamine is useful for the same purposes as the therapies recited by Jordan et al., namely treating depression. One of ordinary skill in the art would reasonably have expected success because ketamine is already known to be useful as an antidepressant.

Thus the invention taken as a whole is *prima facie* obvious.

Claims 3-5, 10-15, 20, 28, 37, and 50-52 are rejected under 35 U.S.C. 103(a) as being unpatentable over Theobald et al. (US patent publication 2003/0049308, first published as PCT international publication WO01/80837)

Theobald et al. discloses a transdermal or transmucosal patch comprising nicotine and a further active substance, that is useful for treating nicotine dependency, for nicotine substitution, or for disaccustoming smokers. (p. 1, paragraphs 0002, 0003, and 0009) The additional active agent can include antidepressants or neuroleptics

(antipsychotics), for example chlorpromazine, perphenazine, sulpride, clozapine, clomipramine, doxepin, risperidone, paroxetine, or fluvoxamine. (p. 2, paragraphs 0015-0017) Theobald et al. does not explicitly exemplify a method comprising administering said patch comprising nicotine, an antidepressant, and an antipsychotic.

It would have been obvious to one of ordinary skill in the art at the time of the invention to practice the method of Theobald et al. using nicotine in combination with both an antidepressant and an antipsychotic. One of ordinary skill in the art would have been motivated to practice the invention in this manner because each of the additional agents (the antidepressant and the antipsychotic) is revealed individually by Theobald et al. to be useful in combination with nicotine for the treatment of nicotine addiction. Adding both of these agents at once to the disclosed invention is well within the ordinary and routine level of skill in the art and carries a reasonable expectation of success in achieving the desired therapeutic goal.

Thus the invention taken as a whole is *prima facie* obvious.

Response to Arguments

Applicant's arguments submitted March 15, 2010, with respect to the above grounds of rejection have been fully considered and not found to be persuasive to remove the rejections. Arguments are addressed hereinbelow:

Rejection for new matter:

Applicant argues that claims 140, 141, 143, and 144 do not introduce new matter because the specification and the provisional application both disclose discussing risk/benefit alternatives with the patient. However, the applicant has not cited specific passages from the specification or provisional application which disclose these methods. Applicant also requests specifics of exactly which words the examiner objects to. However, the problem with these claims is not certain specific words but rather the very nature of what is being claimed. These claims are directed toward a method of interacting with a patient, and are really separate and distinct from the actual therapy being administered to the patient. The goal of the pharmacological therapy is to treat depression and reduce the risk of suicide. The goal of the doctor-patient interactions in claims 140, 141, 143, and 144 is to educate the patient as to the reasons for administering a particular therapy.

In the instant case, although the provisional application contains some arguments that are similar to the ones presented in these claims, the arguments in the provisional application appear to be directed toward convincing the audience of health care practitioners to adopt a particular standard of care. While it is of course part of good clinical practice to discuss the rational behind a therapy with the patient, the claims recite certain specific arguments and rationales that the practitioner should make. In effect, these claims are directed toward a method of convincing a patient to comply with a therapy. Convincing those of skill in the art to adopt a particular standard of care is a separate undertaking from convincing a particular patient to comply with that standard of care. It is not clear that the same arguments will be convincing in both

cases, as the concerns of a patient are different than those of a practitioner and the level of knowledge and experience in the art is different as well. Therefore arguments made in the patent specification to convince other skilled practitioners to adopt a standard of care are not seen to provide written description for a method of using those same considerations to educate a patient about a therapy.

Rejection for Enablement:

Applicant's arguments regarding the enablement of the various classes of therapeutic agents recited in instant claims 1-3 have been considered. The rejection of these claims for lacking enablement has been withdrawn as it is concluded that all of the classes of antidepressant compounds recited in the claims are classes of compounds that one skilled in the art would have had access to and been able to use for the treatment of depression based upon these compounds' known pharmacological effects.

Furthermore, regarding the standard of enablement applied to the cited prior art references, the instant claims were rejected for lacking enablement over their full scope. For a claim to be enabled, it must be enabled for every embodiment encompassed by the claims. For example, a claimed method utilizing antidepressants must be enabled for using any possible antidepressant whatsoever in order to be allowed. In the case of a prior art reference, however, a reference is anticipatory if it enables at least one embodiment falling within the claimed method. For example, if the prior art discloses a method using antidepressants, but is only enabled for using serotonin reuptake

inhibitors, it would only be prior art for a method of using serotonin reuptake inhibitors. However, the fact that the prior art lacked enablement for other embodiments would not prevent its being used as prior art for what it was enabled for. This can create the illusion of a double standard, in which a term is rejected as non-enabled over its full scope in a claim but then considered enabled for one specific embodiment in a prior art reference. However, in both cases, the broad genus is considered non-enabled and the specific embodiment is considered enabled.

It is never alleged that previously known antidepressants, for example citalopram, paroxetine, fluoxetine, and so forth, are non-enabled. One skilled in the art would know based on the state of the art that they can be used clinically, whether in Applicant's method or in a prior art method, whether or not a particular reference specifically reiterates all that is known in the art about the compound. Enablement is less clear, however, for broad functionally defined categories of active agent, for example a claim directed toward antidepressants in general. In such a case, one skilled in the art would have to know all different classes of antidepressants and their limitations, side effects, therapeutic indications, drug interactions, and the like, in order to be able to use the full scope of all possible compounds in the invention. Figuring out all of these uncertain factors would require an immense burden of unpredictable experimentation and the discovery and characterization of many new antidepressants. In short, there is a lower standard of enablement for a mention of a specific active agent or combination of active agents (paroxetine) than for a broad functionally defined class of agents, (antidepressants) as it requires no undue or unpredictable experimentation

for one skilled in the art to simply look up a specific compound in the primary literature or in other reference materials in order to confirm that it possesses therapeutic activity. Of course the recitation of a seemingly absurd embodiment (e.g. treating depression with aspirin) would lack enablement unless the reference gives specific reasons to believe that the embodiment is enabled, either by providing a plausible theoretical basis or convincing experimental data for the embodiment.

Because all of the prior art references make mention of specific active agents which are already known to those skilled in the art, they are enabled as prior art at least for those specific agents.

Prior art rejections:

In the case of the Theobald reference, the reference is considered to be enabled for the specific antidepressants and antipsychotics recited in the reference, regardless of whether the reference is enabled for the broad classes of antipsychotics and antidepressants generally. In considering the eight Wands factors mentioned in previous office actions, the teachings of the prior art, the level of skill in the art, and the predictability of the art are sufficient in the pharmaceutical art that one skilled in the art could look up these compounds and determine their therapeutic indications, drug interactions, optimal doses, and so forth. The reference itself does not need to spell all of these things out in full detail.

Regarding the Jordan reference, it is repeated that the bar for enabling a specific compound or structurally related set of compounds is lower than that needed to enable a broad functionally defined class of compounds. Considering that a convincing line of reasoning has been established (by analogy with gepirone) that 5HT1A agonism could treat depression, it would not require an undue burden of unpredictable experimentation to determine whether the compounds of Jordan et al. had an antidepressant effect, for example using animal models such as the forced swim test or chronic mild stress model. Enablement does not require that a compound have passed clinical trials so long as the amount of experimentation needed to practice the invention is merely routine verification of facts for which evidence already exists.

Regarding the Chappell et al. reference, Applicant argues that the reference does not address the secondary factors recited in the claims such as protecting against the development of tolerance toward antidepressants, avoiding a paradoxical effect of said antidepressant sensitizing said patients to said depression, avoiding worsening of said depression from said antidepressant, treating worsening of said depression from said antidepressant and said antidepressant causing suicidal ideation, these limitations do not further limit the claim because they are not manifest in any actual concrete limitation of the method steps. For example, a limitation on the patient population (e.g. treatment resistant or non-treatment resistant patients), a specific dosage level, or a particular timing of administration, or co-administration with a particular second active agent, are all concrete limitations on the breadth of the claimed method. The instant

claims, for example, clearly do not encompass administering antidepressants and antipsychotics to psychotic patients. Neither do they encompass antidepressant monotherapy. However, what is the concrete difference between the actual method steps undertaken in a method where the practitioner intends to avoid the paradoxical effect of said antidepressant sensitizing said patients to said depression and a method where the practitioner does not intend said effect? If a limitation is not manifest in the actual positive actions taken while performing the method, it does not further limit the claims, as purely mental processes are not patentable.

Factors involved in a determination of obviousness:

While the cited prior art references have been addressed previously, the general rationale behind the finding of obviousness is presented here. The factual inquiries set forth in *Graham* v. *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

The scope and contents of the prior art - antipsychotic agents including atypical antipsychotics are known in the art as being usable for treating depression, typically in combination with an antidepressant, as described in the aforementioned references. The most common use of this combination is in treatment resistant, psychotic, or bipolar

depression, but several patent references make mention of unipolar depression or major depressive disorder as a broad category which can be treated by antipsychotic therapy, for example the reference Howard US2002/0123490.

The differences between the prior art and the claims - none of the prior art references specifically recommend using antipsychotics as initial therapy in a treatment-naive non-psychotic depressed patient who has not previously failed to respond to antidepressant monotherapy. Rather the prior art is silent as to where in the treatment regimen the antipsychotic should be introduced.

The level of ordinary skill in the art - A typical practitioner is skilled in the pharmacological treatment of psychiatric disorders and is familiar with the available literature on psychiatric drugs such as antidepressants and antipsychotics. Furthermore, although these drugs are approved for certain specific indications, one skilled in the art is capable of using them off-label if a suitable rationale exists for doing so, and can perform cost-benefit analysis to determine if the expected benefit from such therapy outweighs the risks in a particular patient. The question as to which therapeutic approach to try first falls within such a cost-benefit analysis.

Objective evidence indicating obviousness or non-obviousness in the application - The application contains a lengthy discussion of the treatment of depression and the inadequacies of current treatment guidelines, particularly as regards the incidence of suicide. While the evidence indicates a clear need for an improved treatment of depression, the application does not in fact provide data showing that the claimed treatment strategy would in fact constitute an improvement over the prior art. While this

might be the case, until proven by factual data, it is insufficient to provide evidence of secondary considerations in favor of patentability.

Secondary Considerations:

Applicant has repeatedly made the argument that the failure of those skilled in the art to actually practice the invention indicates that the invention is not obvious. Applicant's reasoning appears to be the following:

a) Those of ordinary skill in the art are concerned about the risk of suicide in depressed patients and will use the best available therapy to prevent suicide.

b) The claimed method is clearly superior to the current standard of care for treating depression.

c) Those of ordinary skill in the art do not in fact use the claimed invention in clinical practice.

therefore:

d) The claimed invention is not available (i.e. non-obvious) to those of ordinary skill in the art, or else they are unaware that it is superior to the current standard of care.

In technical terms, Applicant is alleging that the claimed invention satisfies a long-felt unsolved need or that it has an unexpected benefit over the prior art. Both of these arguments can be used to overcome a finding of *prima facie* obviousness. However, either of these findings requires evidence that the claimed invention actually

solves the long-felt need or produces the alleged unexpected results, in order to establish part b) of the above syllogism. After all, if an invention is not superior to the prior art it is not surprising if it is not used in clinical practice. There is nothing surprising about the failure of those in the art to use a method that is not superior to the present standard of care.

Applicant's disclosure gives arguments as to why an antipsychotic might augment treatment of depression. However it provides no clinical data to establish whether or not this hypothesized effect is in fact real. Therefore Applicant has not demonstrated unexpected results or satisfaction of a long-felt need. Since Applicant appears to be a skilled practitioner in the art, it is possible that Applicant has actually treated as significant number of patients off-label using the claimed therapeutic method. If this is the case, and the results obtained were clearly superior to those seen in the prior art for the current standard of care, (e.g. antidepressant monotherapy) then an affidavit or declaration under 37 CFR 1.132 summarizing the results obtained in Applicant's own practice and comparing them to what has been observed in the prior art, for example in clinical trials of antidepressant monotherapy, could suffice to establish unexpected results and the satisfaction of a long-felt need. Such results could take the form of an observation of reduced suicidality, faster onset of antidepressant effect, or improved response rate, for example.

Furthermore, a *prima facie* case of obviousness can be overcome if the prior art teaches away from modifying the prior art in the claimed manner. In the instant case,

the prior art teaches an antidepressant effect for antipsychotic medications or combinations of these medications with antidepressants. However as mentioned previously the prior art does not specifically recommend using these agents as an initial therapy. Therefore if it were established that he prior art specifically criticized or discouraged using antipsychotics as initial therapy, this could overcome the finding of obviousness. It is suggested that if Applicant is aware of publications representative of the state of the prior art, for example clinical guidelines or review articles, that specifically disparage or criticize the use of antipsychotics as initial therapy for non-psychotic depression, that submitting these publications in an information disclosure statement could overcome the finding of obviousness if the references are sufficient to establish a widespread consensus in the art at the time of filing against using the claimed invention as initial therapy.

It is also suggested that if such evidence is introduced, the claims may have to be amended so as to be commensurate in scope with the evidence. For example, if the evidence concerns only the use of one particular class of antidepressant, such as serotonin reuptake inhibitors, it may serve to prove non-obviousness only for claims drawn specifically to that particular class of drugs.

If Applicant considers either of these approaches to be feasible for overcoming the obviousness rejections, it is suggested that he contact the examiner to discuss the

specific contents of such a declaration of information disclosure statement before filing any further amendment in this application.

Conclusion

No claims are allowed in this application.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ERIC S. OLSON whose telephone number is (571)272-9051. The examiner can normally be reached on Monday-Friday, 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shaojia Anna Jiang can be reached on (571)272-0627. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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/Eric S Olson/

Examiner, Art Unit 1623
6/4/2010